1. To determine the extent, size, and major organ involvement by metastatic cancer to decide proper patient selection for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).
2. **Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy** Upon determining patient fitness for surgery with selection driven by feasibility criteria, CRS is commonly performed through an open abdominal wall incision approach along with perioperative intraperitoneal chemotherapy. This novel treatment option became a reality for surgeons through the extensive work of Dr. Sugarbacker[38] and his suggested surgical techniques. Cytoreductive surgery includes peritonectomy and individualized manual resection of the tumor lesions from different areas of the abdominal wall and mesentery. Peritonectomy now classifies as a curative treatment method for patients with peritoneal carcinomatosis, with the latter viewed as the locoregional spread instead of systemic disease. The usual surgical intention for any cancer treatment is the removal of all cancer cells through en-block resections with clear margins. However, for peritoneal carcinomatosis, it is highly difficult to achieve the complete removal of malignant cells. The idea behind cytoreduction is to reach complete removal of any macroscopic lesions, and the simultaneous use of HIPEC would potentially remove microscopic cancer lesions.[39][40] This technical approach has shown tremendous survival benefits along with disease-free survival and improved quality of life in patients. Currently, CRS combined with HIPEC is a first-line treatment for appendiceal and colorectal cancer-related PM.[41][42] It has also shown a promising role in ovarian, gastric, and neuroendocrine tumors.[43][8][44]

3. **Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)**This newer innovative therapeutic intervention has potential use in patients with extensive peritoneal carcinomatosis who may be deemed unresectable or unfit for surgery. The basis for aerosol chemotherapy is the premise that the intraabdominal application of chemotherapeutic drugs under pressure could potentially enhance tissue penetration and increases distribution.[45]It has also been found to have superior benefits of drug delivery to tumor tissue with a significant effect on tumor regression than conventional intraperitoneal chemotherapy or systemic chemotherapy.[46] This treatment option is beneficial in patients with extraperitoneal metastases in which this method could work as an effective palliative treatment option. Further ongoing prospective trials will decide on its future role and regular use.

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https://journals.lww.com/oncology-times/fulltext/2020/11050/a_unique_technique_to_treat_peritoneal.6.aspx
OR GERMANY

https://www.docwirenews.com/docwire-pick/hem-onc-picks/intraperitoneal-paclitaxel-addition-may-be-beneficial-for-patients-with-pancreatic-cancer-and-peritoneal-metastasis/
TIME TO GOTO JAPAN?

TRIALS
https://www.clinicaltrials.gov/ct2/show/NCT02600949?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=58

https://www.clinicaltrials.gov/ct2/show/NCT04852367?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=76

https://www.clinicaltrials.gov/ct2/show/NCT03267316?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=78

https://www.clinicaltrials.gov/ct2/show/NCT04976634?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=79

https://www.clinicaltrials.gov/ct2/show/NCT03608631?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=83

https://www.clinicaltrials.gov/ct2/show/NCT02744287?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=85

https://www.clinicaltrials.gov/ct2/show/NCT04887805?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=87

https://www.clinicaltrials.gov/ct2/show/NCT04111172?recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=3&rank=92

https://www.clinicaltrials.gov/ct2/show/NCT02757859?term=PERITONEAL&recrs=a&cond=PDAC+-+Pancreatic+Ductal+Adenocarcinoma&draw=2&rank=1

tyrosine kinase inhibitor **(TY-ruh-seen KY-nays in-HIH-bih-ter) listen**
A substance that blocks the action of enzymes called tyrosine kinases. Tyrosine kinases are a part of many cell functions, including cell signaling, growth, and division. These enzymes may be too active or found at high levels in some types of cancer cells, and blocking them may help keep cancer cells from growing. Some tyrosine kinase inhibitors are used to treat cancer. They are a type of targeted therapy.

erlotinib hydrochloride **(er-LOH-tih-nib HY-droh-KLOR-ide) listen**

A drug used alone to treat certain types of non-small cell lung cancer and with gemcitabine hydrochloride to treat certain types of pancreatic cancer. It is also being studied in the treatment of other types of cancer. Erlotinib hydrochloride blocks a protein called EGFR, which may help keep cancer cells from growing. It is a type of EGFR tyrosine kinase inhibitor. Also called CP-358,774, OSI-774, and Tarceva.

Abstract: Activating mutations in RAS family proteins are found in ~25% of all human cancers. Different solid tumors are correlated with mutations in certain isoforms of RAS, with Kirsten RAS (KRAS) being the most frequently mutated isoform. Historically, KRAS has been acknowledged as "undruggable", largely because the RAS proteins do not appear to present suitable pockets to which small inhibitory molecules can bind. However, this scenario has changed over the last years with the advent of novel KRAS inhibitors. In this review, we describe the role of KRAS mutation across different solid tumors, providing data on novel KRAS inhibitors currently under development and an updated overview of ongoing research in this field. A literature search was performed to select papers, abstracts, and oral presentation on KRAS inhibitory strategies in KRAS mutated solid tumors. Overall, the most promising therapeutic results have been obtained with molecules targeting KRAS G12C, thus paving the way for a significant therapeutic improvement in non-small cell lung cancer. Unfortunately, KRAS G12C mutation is rather uncommon in other solid tumors, namely pancreatic ductal adenocarcinoma, and colorectal cancer. Several combination strategies are currently under evaluation in clinical trials, to bypass the resistance mechanisms responsible for the intrinsic resistance of mutated KRAS to the main therapeutic strategies adopted to date. Results suggest that the therapeutic scenario of KRAS has started to change, and further research will bring therapeutic results in this field.

On **May 28**, the Food and Drug Administration (FDA) granted accelerated approval to the first KRAS-blocking drug, called sotorasib (Lumakras)

https://www.pancan.org/news/5-things-to-know-about-targeting-mutant-kras-in-pancreatic-cancer/

Over the next five years, this sample was fractionated, and the most active component was identified. This compound was named Taxol and soon entered large scale biological testing. Taxol was then transferred from the USDA to Bristol-Myers Squibb for commercial development under the generic name Paclitaxel (Figure 5). Paclitaxel soon entered clinical evaluation in combination with Cisplatin, which was approved for use in ovarian cancer patients in 1992. Paclitaxel was next explored as monotherapy in breast cancer and was approved in patients with axillary node involvement in 1994. Paclitaxel was approved as a second-line treatment of AIDS-related Kaposi's sarcoma in 1997 and in combination with Cisplatin for select cases of non-small cell lung cancer in 2006. Paclitaxel is also used off label to treat several other cancers, including those of the esophagus, stomach, endometrium, cervix, prostate, head and neck, as well as sarcomas, leukemias, and lymphomas (184).

Ferroptosis: Kills cancer cells by depletion of Cysteine (what allows PDAC to thrive). Cysteinase has been approved to treat metabolic d/o, Cystinuria.

CDK inhibitor AT7519 could be used to treat pancreatic cancer patients whose tumors are addicted to mutant KRAS.

Research completed at VCU suggests that some tumors are addicted to KRAS mutations. These tumors are associated with CDK2, CDK7, CDK9 proteins. They found that the most effective drug in pre-clinical experiment was the AT 7519, which inhibits CDK1, 2, 7, & 9.

THUNDER GOD VINE: University of Minnesota- Drs. Rohit Chugh and Ashok Saluja showed that the vine effectively killed pancreatic cancer cells in in vitro and in vivo models. Developed a water soluble triptolide analg called Minnelide.

New tumor-penetrating therapy enhance effects of chemo and spread of disease in mice. University of California San Diego and Moores Cancer Center along with Sanford0Burnham-Prebys Medical Discovery Institute and Columbia Univerity. Dr. Andrew Lowy at UC SD and co-author of the study. iRGD injected into mice with high levels of B5 integrin= increased survival and reduction in the cancer speading to other organs.

Bases and foundations of the treatment of peritoneal carcinomatosis: Review article
J.F. Castro-Mestaa,∗, J.F. González-Guerreroa, P. Barrios-Sánchezb, G. Villarreal-Cavazosa
Peritoneal carcinomatosis refers to a shedding or tumor that spreads to the periton- eal serosa and structures of the abdominal cavity. It is an entity with a poor prognosis. Several conditions can cause this, the most common being colon, rectum, ovary, stomach or appendix cancers, including peritoneal pseudomyxoma, among others. The abdominal cavity invasion is considered a clinical stage IV. For a long time life expectancy of this entity was very short. With the advent of meticulous techniques in cytoreductive surgery (CRS) and hyperthermic intraperi-toneal chemotherapy (HIPEC) the prognosis of patients has changed. In some conditions, these procedures are standard treatments. CRS is a very important prognostic factor; leaving a less residual disease in the patient, the evolution will be better. The HIPEC starts immediately after the surgical event. The hyperthermia increases the cytotoxic effect of antineoplastic drugs. Numerous studies have appeared in medical literature wherein the clear improvement in sur-vival of the affected population is demonstrated. It is essential that a multidisciplinary team participates in the decision for the best treatment option and the maximum clinical benefit of the patients.

Hedgehog pathway, angiogenesis, hyaluronic acid, cancer-associated fibroblasts and associated cytokines.

- rather than a one-size-fits-all approach, anti-angiogenesis targets could be considered as an adjunct for the subgroup of well-vascularized and poorly differentiated tumors.
- Chemo with VEGF blockade resulted in tumor shrinkage with decreased MVD.

- Gemcitabine with PEGPH20 altered the Tumor microenvironment, reduction of tumor size.
- Administration of NOX4 inhibition with setanaxib helped mediate immunotherapy resistance. (Trial NCT04543071)
- IL-6 (SECRETED BY ICAFS) studied to enhance the efficacy of PD-L1 blockage in PDAC. Nab-pacitaxel, part of chemotherapy, in the approved armamentarium, has been shown to disrupt the stroma by decreasing PD-L1 blockade and improve survival outcomes in GEM models and demonstrate increased T cell infiltration.
    - Siltuximad- targets IL-6 shown to be well tolerated. (Trial NCT04191421)
    - Tocilizumab- another IL-6 inhibitor- Trial NCT02767557
    - Leukemia inhibitory factor (LIF) produced by PSCs and stimulated by KRAS mutations. Shown to correlate with responses to chemotherapy and shown to neutralize antibodies combined with gemcitabine inhibiting tumor growth.
    - IL-1 receptor bloackade using Anakinra with FOLFIRINOX showed safety and tolerability (Trial NCT02021422)
    - Trial NCT03086369
    - Oral CCR2 inhibitor with FOLFIRINOX 49% response rate with no increase in pulmonary toxicity.
- Connective tissue growth factor (CTGF) is implicated in promoting fibrosis in PDAC cells[135]. Pamrevlumab, a monoclonal antibody targeting CTGF, in combination with gemcitabine and nab-paclitaxel as neoadjuvant therapy demonstrated a remarkable decrease of 20.6% in size of target lesions in a phase I/II trial[136]. Based on these exciting results, the phase III trial using this combination is now being explored (NCT03941093)[137].
-

For instance, targeting IRAK4 using small molecule kinase inhibitors was shown to reduce stromal fibrosis and potentiate the efficacy of chemotherapy in preclinical mouse models [56,58]. Currently, the IL-1 receptor antagonist Anakinra is being tested in combination with nab-paclitaxel, gemcitabine and cisplatin in patients with resectable or potentially resectable PDAC (NCT 02550327). To date, the results for this clinical trial are pending.

treatment with pamrevlumab (or FG-3019), a humanized monoclonal antibody targeting CTGF, potentiates the effect of gemcitabine by downregulating X-linked inhibitor of apoptosis protein, rather than promoting delivery of gemcitabine[59]. In other PDAC pre-clinical studies pamrevlumab was shown to attenuate tumor growth, metastasis and angiogenesis[60]. These studies collectively suggest that the therapeutic effect of pamrevlumab is predominantly through targeting tumor cells. A phase I/II study evaluated pamrevlumab with gemcitabine and nab-paclitaxel in patients with LAPC. After 6 cycles/months of therapy, more patients treated with pamrevlumab and chemotherapy underwent resection compared to patients receiving chemotherapy only (33.3% *vs* 7.7%). The higher resection rate translated into improved OS (non-estimable *vs* 18.56 mo, $P = 0.0141$). Did not inhibit surgical wound healing or increase post operative adversive outcomes. CURRENT TRIAL (Phase III) NCT03941093

studies showing that higher pre-diagnostic serum vitamin D levels were shown to be associated with better survival in PDAC patients [65], and overwhelming preclinical studies demonstrating protective effects of vitamin D. calcipotriol lowered the expression of low-density lipoprotein receptor-related protein 6 and inhibits autocrine Wnt signaling[68]

Paricalcitol was also shown to impede PDAC cell proliferation by upregulating cell cycle inhibitors p21 (Waf1/CIP1) and p27 (Kip1)[69]. On these premises, multiple phase I or II studies testing the impact of paricalcitol are currently opened. These include in combination with cisplatin, gemcitabine and nab-paclitaxel for patients with treatment-naïve metastatic PDAC (NCT04054362); in combination with hydroxychloroquine, gemcitabine and nab- paclitaxel for patients with treatment-naïve metastatic PDAC (NCT04524702); in combination with 5-FU/Liposomal irinotecan for patients who have progressed through frontline gemcitabine-based therapies (NCT03883919); and in combination with anti-PD-1 (pembrolizumab) as maintenance treatment for patients who have achieved partial response or stable disease for at least two months on chemotherapy (NCT03331562).

treatment with all-trans retinoic acid (ATRA) induced quiescence of PSC, reduced proliferation of PDAC cells and led to increased apoptosis of PDAC cells in part by down-regulating Wnt signaling[71]. Safety and tolerability of the regimen, and diffusion weighted-magnetic resonance imaging identified signals of stromal modulation. Based on these data, the combination of ATRA along with GnP is currently being studied in the Phase II randomized STAR_PAC trial (NCT03307148) enrolling patients with locally advanced or metastatic disease[72].

Pirfenidone is an anti-inflammatory and anti-fibrotic agent that is clinically used for treatment of idiopathic pulmonary fibrosis, however with an unknown mechanism of action. In primary human lung fibroblasts, pirfenidone inhibits proliferation, TGF-β- induced myofibroblast differentiation and pro-collagen expression[73]. Pirfenidone also blocks proliferation, production of collagen, fibronectin and periostin by PSCs *in vitro* and *in vivo*, and potentiates the anti-tumor effect of gemcitabine by reducing stromal fibrosis[74].

Halofunginone (HF) cause resolution of pathologic liver fibrosis. but it also fosters favorable immune response by augmenting cytotoxic T-cells and stimulatory myeloid cells in the tumor stroma

Excessive HA deposition, which is common in PDAC tumors, causes elevated water retention and consequently high interstitial pressure that collapses tumor vasculature and limits delivery of therapeutics[19]

Pluripotent stem cells (PSCs) are promising tools for modern regenerative medicine applications because of their stemness properties, which include unlimited self-renewal and the ability to differentiate into all cell types in the body. Evidence suggests that a rare population of cells within a tumor, termed cancer stem cells (CSCs), exhibit stemness and phenotypic plasticity properties that are primarily responsible for resistance to chemotherapy, radiotherapy, metasta- sis, cancer development, and tumor relapse. Different therapeutic approaches that target CSCs have been developed for tumor eradication. **Lead Researchers: Seyedeh-Nafiseh Hassani snafiseh.hassani@royaninstitute.org; sn.hassani@royan-rc.ac.ir Marzieh Ebrahimi m.ebrahimi@royan-rc.ac.ir**

Yes, there are many types of biomarker tests that can help select cancer treatment. Most biomarker tests used to select cancer treatment look for genetic markers. But some look for proteins or other kinds of markers.

Some tests check for one certain biomarker. Others check for many biomarkers at the same time and may be called multigene tests or panel tests. One example is the Oncotype DX test, which looks at the activity of 21 different genes to predict whether chemotherapy is likely to work for someone with breast cancer.
Some tests are for people with a certain type of cancer, like melanoma. Other tests look for biomarkers that are found in many cancer types, and such tests can be used by people with different kinds of cancer.
Some tests, called whole-exome sequencing, look at all the genes in your cancer. Others, called whole-genome sequencing, look at all the DNA (both genes and outside of genes) in your cancer.
Still other biomarker tests look at the number of genetic changes in your cancer (what's known as tumor mutational burden). This information can help figure out if a type of immunotherapy known as immune checkpoint inhibitors may work for you.
Biomarker tests known as liquid biopsies look in blood or other fluids for biomarkers from cancer cells. There are two liquid biopsy tests approved by the Food and Drug Administration (FDA), called **Guardant360 CDx and FoundationOne Liquid CDx.**

Study in China: Pancreatic cancer is a highly malignant cancer associated with high expression levels of sonic hedgehog signaling molecule (Shh), patched 1 (Ptch1), smoothened frizzled class receptor (Smo) and glioma-associated oncogene family zinc finger 1 (Gli1) in the hedgehog (Hh) signaling pathway. Inhibition of the Hh signaling pathway is a potential therapeutic target for pancreatic cancer. The aim of the present study was to investigate the effects of dauricine in a pancreatic cancer BxPC-3 xenograft animal model and examine the underlying molecular mechanisms through Hh signaling pathway. High-and low-dose dauricine treatment significantly suppressed tumor growth with no concomitant effect on the spleen index. In addition, dauricine induced apoptosis and cell cycle arrest in pancreatic cancer BxPC-3 cells. The inhibitory effects of dauricine on pancreatic cancer may be mediated by the suppression of the Hh signaling pathway, as indicated by the decreases in the gene and protein expression levels of Shh, Ptch1, Smo and Gli1. The effects of dauricine were similar to those of 5-fluorouracil. Dauricine, a naturally occurring alkaloid, may be a potential anticancer agent for the treatment of pancreatic cancer. The study also revealed that mutant KRAS tumors exhibit higher expression levels of Shh and Ihh compared with wild-type KRAS tumors, which suggested that KRAS-mutated tumors may benefit from Hh inhibitors.

Dr. Michael Veeder, an Illinois CancerCare physician on the pancreatic cancer treatment team attended the national meeting where this groundbreaking treatment was announced. He states, "Due to results gathered from the clinical trial POLO (Pancreas Cancer Olaparib Ongoing), we now know that the 5% of people who have an inherited form of pancreatic cancer with BRCA1 and BRCA2 gene alterations benefitted from a maintenance drug olaparib (Lynparza) that inhibits the cancer from multiplying." On December 27th, 2019, this treatment was approved by the FDA (U.S. Food and Drug Administration) and is now available at Illinois CancerCare for central Illinois patients.
This clinical research trial illustrates the importance of genomic testing in pancreatic patients to identify germline mutations including BRCA1, BRCA2, Lynch Syndrome mutations, FAMMM, and others.
Genomic testing in pancreas cancer patients can now direct oncologists to FDA approved targeted therapy.

Results: We found that AIB1 was significantly upregulated in PDAC and associated with its malignancy. Silencing AIB1 impaired hedgehog (Hh) activation by reducing the expression of smoothened (SMO), leading to cell cycle arrest and the inhibition of PDAC cell proliferation. In addition, AIB1, *via* upregulation of integrin αv (ITGAV) expression, promoted extracellular matrix (ECM) signaling, which played an important role in PDAC progression. Further studies showed that AIB1 preferably bound to AP-1 related elements and served as a coactivator for enhancing the transcriptional activity of MafB, which promoted the expression of SMO and ITGAV. PDAC cells with high AIB1 levels were sensitive to Hh signaling inhibitors, suggesting that blocking Hh activation is an effective treatment against PDAC with high AIB1 expression.
Conclusions: These findings reveal that AIB1 is a crucial oncogenic regulator associated with PDAC progression *via* Hh and ECM signaling and suggest potential therapeutic targets for PDAC treatment.

Adding cisplatin to the standard gemcitabine/nab-paclitaxel drug treatment provided a very high rate of tumor shrinkage for patients with advanced pancreatic cancer, according to the results of a pilot clinical trial conducted by the HonorHealth Research Institute and the Translational Genomics Research Institute (TGen). Dr. Daniel Von Hoff- professor and physician who advised the clinical trial.

Oncologist: Dr. Brian M. Wolpin: Dana Faber in Boston: "Elite in Pancreatic Cancer"

- Accepting new patients
- Recent study about the KRAS mutation (which you have)
- **617-632-6942**
- His clinical research consists of co- authoring 184 peer reviewed articles and participating in 86 clinical trials in the past 15 years. In particular, he has co-authored 116 articles and participated in 9 clinical trials in the study of pancreatic cancer.